REMARKS

Claims 1, 2, 4, 5, 8-12, and 27-41 are pending in the application. For the Examiner's convenience all of the pending claims are set forth in Appendix A.

No new matter has been added.

Objection of the Disclosure

The Examiner has objected to the specification because the ATCC accession number is not indicated.

Applicants respectfully submit that, pursuant to *In re Lundak*, Applicants have the right to make a deposit of a plasmid containing a nucleotide sequence encoding the NIP2b, NIP2cL, and NIP2cS molecules of the present invention, prior to issuance of the application. *In re Lundak* 723 F2.d 1216, 227 USPQ 90 (Fed. Cir. 1985). Accordingly, Applicants reserve the right to amend the specification as originally filed to include the ATCC Deposit information for these molecules prior to issuance of the application.

The examiner has also objected to the incorporation of embedded hyperlinks and/or other forms of browser-executable code in the specification. All references to browser executable code have been removed. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this objection to the specification.

Finally, the examiner has objected to the incorporation by reference of various scientific publications throughout the specification.

Applicants respectfully submit that the incorporation of non-essential subject matter from a non-patent publication, *e.g.*, a published journal article, may be incorporated by reference. MPEP § 608.01(p).

Applicants further submit that, as required by MPEP § 608.01(p), the present specification has been amended to recite the specific sections from the Trump *et al.* and Lee *et al.* references found at page 11, lines 27-29 of the specification. Applicants submit that the

amendatory material consists of the same material incorporated by reference in the instant specification.

Rejection of Claims 1-2, 4-5, 8-12, 29-39, and 40-41 Under 35 U.S.C. § 101

The Examiner has rejected claims 1-2, 4-5, 8-12, 29-39, and 40-41 under 35 U.S.C. § 101 because, according to the Examiner, "the claimed invention is not supported by either a specific and substantial utility or a well established utility." In particular, the Examiner is of the opinion that

> [a]ll function of the encoded proteins is by inference; no information is provided that the instant genes & constructs do indeed regulate apoptosis under any conditions. A starting material that can only be used to produce a final product does not have a substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case none of the proteins that are to be produced as final products resulting from processes involving the claimed cDNA have asserted or identified specific and substantial utilities. The research contemplated by Applicants to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of the protein itself or the mechanisms in which the protein is involved does not define a "real world" context of use. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the cDNA compounds such that another non-asserted utility would be well established for the compounds.

The Examiner further argues that "[n]o specific properties of the claimed protein are discussed, nor are there any specific diseases discussed which can be treated by administration of the protein. "

Applicants respectfully traverse the foregoing rejection for the following reasons. Applicants respectfully submit that a specific and substantial utility has clearly been set forth in the instant specification that would have been credible to one of skill in the art at the time of invention. Contrary to the Examiner's assertions, specific properties of the NIP polypeptide are discussed and specific diseases which may be treated by the administration of the NIP molecules are disclosed in the instant specification. Specifically, the present specification teaches that the

NIP molecules of the present invention play a role in apoptosis and that, therefore, these molecules provide novel diagnostic targets and therapeutic agents for disorders characterized by deregulated programmed cell death such as Alzheimers disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, Jakob-Creutzfieldt disease, or AIDS related dementias; ischemic injury, *e.g.*, myocardial infarction, stroke, or reperfusion injury; or profilerative disorders, *e.g.*, cancer (see page 12, lines 1-5 of the specification). It is evident, based on Applicants' disclosure of the properties of the NIP2 molecules of the present invention and the knowledge of one skill in the art, that a specific, substantial, and credible utility was immediately apparent for the present invention: *the use of the claimed invention to modulate apoptosis.*

The Examiner also argues that

> [b]ecause the art is cognizant that structural similarities in cloned genes or their encoded proteins do not *a priori* indicate functional similarities (see, e.g., Doerks, et al., Smith et al., Brenner et al., and Bork, et al.), further doubt is cast upon the utility and function of these disclosed sequences. Special attention is given to Brenner, (page 132, column 2, lines 28-33) in that sequence homology does not necessarily equate with function.

Applicants respectfully submit that while examples exist of polypeptide families wherein individual members have distinct, even opposite, biological activities, growing databases and improved search techniques, particularly the iterated PSI-BLAST tool, has yielded substantial improvement in secondary structure prediction accuracy. According to Rost, a copy of which is submitted herewith as Appendix B, "[s]econdary structure predictions are increasingly becoming the work horse for numerous methods aimed at predicting protein structure and function." Burkhard Rost, *Review: Protein Secondary Structure prediction Continues to Rise* (2001) J. Structural Biology 134: 204-218.

Moreover, as the Examiner is aware, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340

F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). "Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true." M.P.E.P. §2164.07. Based on the ample teachings in Applicants' specification regarding the role and importance of NIP molecules in apoptosis, Applicants respectfully submit that a person of ordinary skill in the art would conclude that Applicants' asserted utility is more likely than not true, which is all that is required under 35 U.S.C. §101.

As indicated by Rost (*supra*) "[s]tate-of-the-art methods now reach sustained levels of 76% [function] prediction accuracy." Applicants have utilized these state-of-the-art methods to assess protein function and have demonstrated that the asserted utility is "more likely than not true."

In view of the foregoing, it is evident that Applicants' invention has a specific, substantial, and credible utility that would have been readily apparent to one of skill in the art. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing section 101 rejection of claims 1-2, 4-5, 8-12, 29-39, and 40-41.

Rejection of Claims 1-2, 4-5, 8-12, 29-39, and 40-41 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-2, 4-5, 8-12, 29-39, and 40-41 under 35 U.S.C. §112, first paragraph because, according to the Examiner, "since the claimed invention is not supported by either a specific and substantial utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

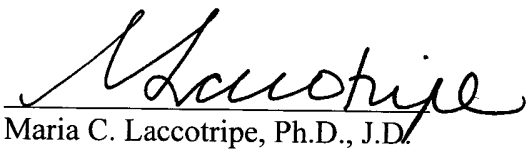
Applicants respectfully traverse the foregoing rejection because, as indicated above, the claimed invention has a well established utility and, thus, one of skill in the art would know how to use the claimed invention. Moreover, Applicants' specification discloses *ample* guidance as to how one of skill in the art would use the claimed invention (see, for example, the screening assays, the diagnostic assays, the prognostic assays, and the methods of treatment, *e.g.*, therapeutic and prophylactic, taught by Applicants at page 47, line 28, through page 71, line 29 of the specification).

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing section 112, first paragraph rejection.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Agent would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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Agent for Applicants
Limited Recognition Under 37 C.F.R. §10.9(b)

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Dated: October 18, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Page 11, lines 27-29:

~~For a detailed description of programmed cell death see Trump B.F. et al. (1995) *FASEB J.* 9: 219-228 and Lee S. (1993) *Curr. Opin. Cell Biol.* 5: 286-291, the contents of which are incorporated herein by reference~~. Trump *et al.* teach that "$[Ca]^{2+}$ plays a very important role in the pathogenesis of cell injury and cell death." They conclude, based on the experiments in their laboratory as well as the current knowledge in the field, that "modulation of $[Ca]^{2+}$ represents a major mechanism in the pathogenesis of prelethal cellular reactions to the injury as well as to the mechanisms involved in both accidental and programmed cell death (Trump *et al.* (1995) *FASEB J.* 9:219-228). These statements are supported by Lee *et al.* who teach that "increased levels of cytosolic calcium may trigger secondary events resulting from the activation of other Ca^{2+} dependent events culminating in cell death (Lee *et al.* (1993) *Curr. Opin. Cell Biol.* 5:286-291)."

Page 10, lines 3-10:

In another embodiment, a NIP2b, NIP2cL, and NIP2cS of the present invention is identified based on the presence of a "calcium-binding domain" in the protein or corresponding nucleic acid molecule. As used herein, the term "calcium-binding domain" includes a protein domain having an amino acid sequence of about 110 amino acids which has the capacity to bind calcium. Preferably, a calcium binding domain includes a protein domain which is at least 50, 60, 70, 80, 90, or 100 amino acid residues in length and which has the capacity to bind calcium. The calcium-binding domain HMM has been assigned the PFAM Accession MILPAT0063 ~~(http://genome.wustl.edu/Pfam/WWWdata/EGF.html)~~ (Bateman, A., et al (2000) NAR 28: 263-266).

Page 10, lines 11-28:

To identify the presence of a calcium-binding domain in a NIP2b, NIP2cL, or NIP2cS protein, and make the determination that a protein of interest has a particular profile, the amino acid sequence of the protein is searched against a database of HMMs (e.g., the Pfam database, release 2.1) using the default parameters ~~(http://www.sanger.ac.uk/Software/Pfam/HMM_search)~~ (Bateman, A., et al (2000) NAR 28: 263-266). For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default

program for MILPAT0063 and a score of 15 is the default threshold score for determining a hit. Alternatively, the threshold score for determining a hit can be lowered (e.g., to 8 bits). A description of the Pfam database can be found in Sonhammer *et al.* (1997) *Proteins* 28(3)405-420 and a detailed description of HMMs can be found, for example, in Gribskov *et al.*(1990) *Meth. Enzymol.* 183:146-159; Gribskov *et al.*(1987) *Proc. Natl. Acad. Sci. USA* 84:4355-4358; Krogh *et al.*(1994) *J. Mol. Biol.* 235:1501-1531; and Stultz *et al.*(1993) *Protein Sci.* 2:305-314, the contents of which are incorporated herein by reference. A search was performed against the HMM database resulting in the identification of a calcium-binding domain in the amino acid sequence of NIP2cL (SEQ ID NO: 5) at about residues 55-160 of SEQ ID NO:5 and NIP2cS (SEQ ID NO:8) at about residues 59-96 of SEQ ID NO:8. The results of the searches are set forth in Figures 8 and 9, respectively.

Page 10, lines 33-38; Page 11, lines 1-11:

In another embodiment, a NIP2b, NIP2cL, and NIP2cS of the present invention is identified based on the presence of a "4 transmembrane segment integral membrane protein domain" in the protein or corresponding nucleic acid molecule. As used herein, the term "4 transmembrane segment integral membrane protein domain" includes a protein domain having an amino acid sequence of about 50 amino acid residues and having a bit score for the alignment of the sequence to the "4 transmembrane segment integral membrane protein domain" (HMM) of at least 1 or greater. Preferably the term "4 transmembrane segment integral membrane protein domain" includes a protein domain having an amino acid sequence of about 60, 70, 80, or 90 amino acids and having a bit score for the alignment of the sequence to the "4 transmembrane segment integral membrane protein domain" (HMM) of at least 2, preferably 3-10, more preferably 10-30, more preferably 30-50, even more preferably 50-75, 75-100, 100-200 or greater. The "4 transmembrane segment integral membrane protein domain" HMM has been assigned the PFAM Accession PF00335 ~~(http://genome.wustl.edu/Pfam/WWWdata/EGF.html)~~ (Bateman, A., et al (2000) NAR 28: 263-266). A search was performed against the HMM database, as described herein, resulting in the identification of a "4 transmembrane segment integral membrane protein domain" in the amino acid sequence of NIP2b (SEQ ID NO:2) at about residues 253 to 293. The results of the search are set forth in Figure 7.

Page 28, lines 22-35:

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP

program in the GCG software package ~~(available at http://www.gcg.com)~~(available from Accelrys, Inc., San Diego, CA), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package ~~(available at http://www.gcg.com)~~(available from Accelrys, Inc., San Diego, CA), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

Page 28 lines 35-38; Page 29, lines 1-10:

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to NIP2b, NIP2cL, and NIP2cS nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to NIP2b, NIP2cL, and NIP2cS protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. ~~See http://www.ncbi.nlm.nih.gov~~.(Altschul, S.F., et al. (1990)J. Mol. Biol. 215:403-410; Altschul, S.F., et al. (1997) Nucleic Acids Res. 25:3389-3402).